

Selective Kv1.5 Blockers: Development of (*R*)-1-(Methylsulfonylamino)-3-[2-(4-methoxyphenyl)ethyl]-4-(4-methoxyphenyl)-2-imidazolidinone (KVI-020/WYE-160020) as a Potential Treatment for Atrial Arrhythmia

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Received July 14, 2009

Abstract: Atrial fibrillation is the most prevalent form of cardiac arrhythmia. Current treatments extend the atrial effective refractory period by nonselective blockade of cardiac ion channels. An alternative approach selectively targeting the Kv1.5 ion channel offers the opportunity for therapeutic benefit with decreased risk of adverse cardiovascular events. KVI-020 (**4g**) successfully demonstrated antiarrhythmic efficacy in a canine arrhythmia model, and these findings support its utility as an antiarrhythmic agent.

Atrial fibrillation (AF), the most prevalent form of cardiac arrhythmia, contributes to increased risk of heart failure, ischemia, morbidity, and mortality.¹ Current therapies extend the atrial action potential duration and effective refractory period by nonselective blockade of cardiac ion channels. Amiodarone (**1**, Figure 1) increases the refractory period and slows the intracardiac action potential conduction via potassium and sodium channel blockade. Its utility is limited by its actions on the thyroid and the risk of ventricular arrhythmia via hERG blockade.² Dronedarone (structure not shown), an amiodarone analogue recently approved for AF, has decreased thyroid activity but is less efficacious than the parent compound (**1**) in AF patients.³ Vernakalant (**2**) is currently in phase III clinical trials for atrial arrhythmia; its mechanisms of action include equipotent blockade of Kv1.5, hERG, and Nav1.5.⁴

Safety risks associated with current and emerging therapies might be mitigated with a selective ion channel blocker.⁵ Elimination of hERG channel activity is of particular interest. hERG is expressed in the atria and ventricle and is associated with plateau and late stage repolarization. Blockade of the hERG channel has been directly associated with ventricular action potential prolongation, QT prolongation, ventricular arrhythmia, torsade de pointes, and ultimately sudden cardiac death.⁶

In contrast to hERG, the Kv1.5 voltage-gated potassium channel plays a critical role in the early and plateau phases of repolarization of atrial cells but has no function in ventricular

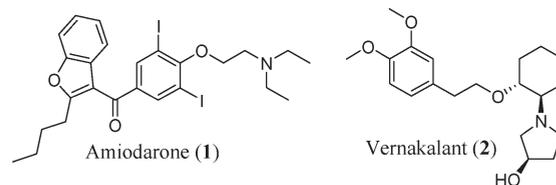


Figure 1. Amiodarone (**1**) and vernakalant (**2**).

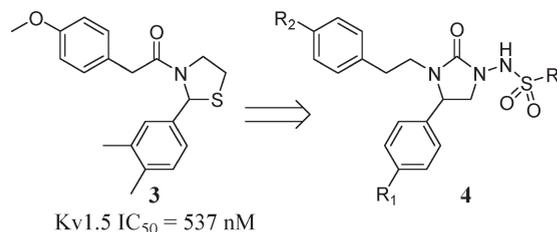


Figure 2. Acylthiazolidine (**3**) and 2-amino-2-imidazolidinones (**4**).

cells.⁷ It is an attractive target for the treatment of atrial arrhythmia. The absence of Kv1.5 in human ventricular cells should lead to a decreased risk of ventricular events and improved therapeutic margins.

A series of acylthiazolidines (e.g., **3**) was disclosed as Kv1.5 blockers (Figure 2).⁸ Our design objective was to preserve the relative disposition of the aryl rings in the pharmacophore presented by **3** while replacing the metabolically labile 1,3-thiazolidine ring with the more stable imidazolidinone system. The development of a series of 2-amino-2-imidazolidinones (**4**) as potent Kv1.5 blockers useful for the prevention of atrial arrhythmias will be described.

Compounds **4** were prepared in a six-step synthesis from readily available nitrostyrenes (**I**) as shown in Scheme 1. Michael addition with an appropriately substituted amine (**II**) followed by reduction provided diamines **III**. Cyclization with 1,1'-carbonyldiimidazole provided the core 2-imidazolidinones (**IV**). The penultimate 2-amino-2-imidazolidinones (**V**) were generated in a one-pot, two-step nitrosation/reduction sequence. Sulfonylation with a sulfonyl chloride then provided the target compounds (**4**).

Compounds were assessed for Kv1.5 potency on an automated electrophysiological patch clamp platform using cloned human Kv1.5 channels expressed in CHO cells, with follow-up assessment for hERG activity. Cross-reactivity data were obtained for the important cardiovascular channels Nav1.5,⁹ Cav1.2,¹⁰ and Cav1.3.¹¹ In addition, important ion channels with high homology to Kv1.5 were examined, including Kv1.1, a neuronal target,¹² Kv1.3, a channel found in T-cells,¹³ and Kv4.3, a cardiac channel involved in the early phase of repolarization of both chambers of the heart.¹⁴

An early comparator compound (**4a**) demonstrated Kv1.5 potency ($IC_{50} = 610$ nM) and hERG selectivity (26-fold) but limited aqueous solubility (pH 7.4 buffer) and human microsomal stability, as well as measurable Cyp 3A4 inhibition (Table 1). Deletion of the 3-methyl substituent (**4b**) improved Kv1.5 potency ($IC_{50} = 240$ nM) and hERG selectivity (47-fold), but only modest pharmaceutical profiling improvements were observed. Incorporation of a 4-cyclopropyl group

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Scheme 1. General Synthesis of 4

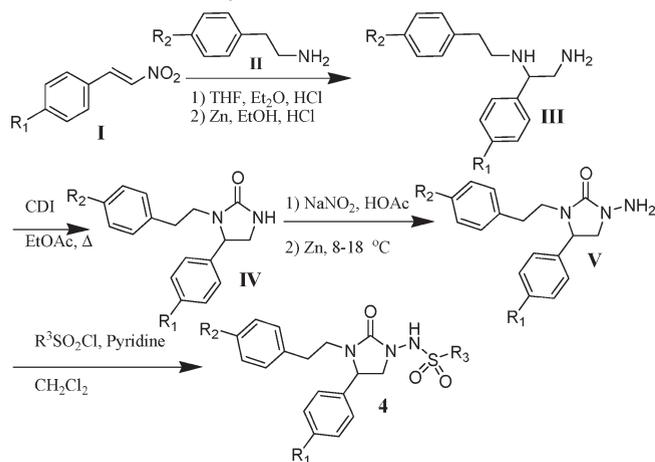


Table 1. Modified Lower Aryl Ring, 4a-i

R ₁	IW IC ₅₀ (nM)		aq sol ^c (μg/mL)	stability (t _{1/2} , min) ^d	Cyp 3A4, % inhib at 3 μM ^e
	Kv1.5 ^a	hERG ^b			
4a 3,4-di-Me	610 ± 101	15800	17	13	77
4b 4-Me	240 ± 57	11200	42	18	58
4c 4-cycprop	160 ± 21	8400	1	30	78
4d 4-Cl	200 ± 66	8700	4	30	27
4e 4-CF ₃	250 ± 72	9100	13	30	67
4f (S)-4-OMe	330 ± 66	26700	100	16	50
4g (R)-4-OMe	480 ± 44	15100	65	30	45
4h 4- <i>i</i> -PrO	240 ± 60	17000	26	30	53
4i 4-O(CH ₂) ₂ OMe	7450 ± 1950	33000	100	30	50

^aKv1.5 IC₅₀ determined on an IonWorks platform with CHO-hKv1.5. ^bhERG IC₅₀ values were obtained from Essen Instruments Inc. ^cpH 7.4 buffer, direct UV method. ^dHuman liver microsomal. ^eFluorescent method.¹⁶

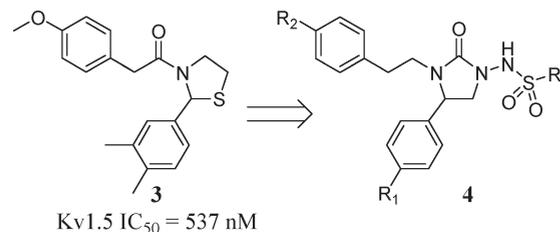
(4c) improved Kv1.5 potency (IC₅₀ = 160 nM), increased hERG selectivity (53-fold), and also increased human microsomal stability (t_{1/2} = 30 min); however, aqueous solubility remained an issue. Electron withdrawing substituents (4d and 4e) also afforded potent inhibitors (Kv1.5 IC₅₀ = 200 and 250 nM) with improved microsomal stability (t_{1/2} = 30 min), but aqueous solubility remained an issue. Incorporation of a 4-methoxy substituent (4f and 4g) provided potent Kv1.5 blockade (Kv1.5 IC₅₀ = 480 and 330 nM, respectively), hERG selectivity (81- and 31-fold, respectively), with improved aqueous solubility (100 and 65 μg/mL, respectively). Human microsomal stability increased for 4f (t_{1/2} = 30 min) but not 4g (t_{1/2} = 16 min). Increasing the steric bulk of the ether to an isopropyl ether (4h) provided improved Kv1.5 potency (IC₅₀ = 240 nM), increased hERG selectivity (71-fold), and also increased human microsomal stability (t_{1/2} = 30 min); however, aqueous solubility decreased (26 μg/mL). Solubilization and metabolic stabilization were

Table 2. Modified Upper Side Chain, 4f,g,j-m

R	n	IW IC ₅₀ (nM)		aq sol ^c (μg/mL)	stability (t _{1/2} , min) ^d	Cyp 3A4 % inhib at 3 μM ^e
		Kv1.5 ^a	hERG ^b			
4f (S)-4-OMe	1	330 ± 66	26700	100	16	50
4g (R)-4-OMe	1	480 ± 44	15100	65	30	45
4j (S)-4-OMe	2	100 ± 40	14100	18	29	84
4k (R)-4-OMe	2	560 ± 9	14300	15	12	50
4l OEt	1	770 ± 238	12200	43	17	4
4m OCF ₃	1	520 ± 110	5600	4	15	53

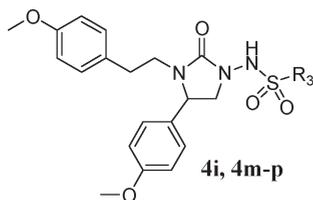
^aKv1.5 IC₅₀ determined on an IonWorks platform with CHO-hKv1.5. ^bhERG IC₅₀ values were obtained from Essen Instruments Inc. ^cpH 7.4 buffer, direct UV method. ^dHuman liver microsomal.¹⁵ ^eFluorescent method.¹⁶

achieved by incorporation of a 4-methoxyethoxy group (4i), but Kv1.5 activity was reduced (IC₅₀ = 2130 nM).



Modification of the upper side chain was then examined, as shown in Table 2. Chain elongation from two to three carbon atoms provided mixed results. The (S)-isomer (4j) demonstrated improved Kv1.5 potency (IC₅₀ = 100 nM) and hERG selectivity (141-fold), but aqueous solubility decreased (18 μg/mL) and Cyp 3A4 inhibition increased (84% at 3 μM). The (R)-isomer (4k) possessed comparable Kv1.5 potency (IC₅₀ = 560 nM) and hERG selectivity (26-fold) relative to the original lead (4a), but microsomal stability and aqueous solubility were not improved. Incorporation of a trifluoromethoxy group in place of a methoxy group or extension of the ether moiety to an ethoxy group reduced hERG selectivity (4l and 4m, 16-fold and 11-fold, respectively).

In the sulfonyl hydrazide region of the pharmacophore (R³), Kv1.5 activity was maintained with a range of different functionality (Table 3). A benzyl group was tolerated (4n, Kv1.5 IC₅₀ = 340 nM), but hERG selectivity (13-fold) and microsomal stability (t_{1/2} = 3 min) decreased. The nitrile derivative 4o provided excellent Kv1.5 potency (IC₅₀ = 230 nM), hERG selectivity (143 fold), and increased aqueous solubility (100 μg/mL), but microsomal stability decreased relative to 4g (t_{1/2} = 21 min). Monofluorination of the sulfonyl hydrazide (4p) also led to decreased microsomal stability (t_{1/2} = 13 min). The 3-pyridyl analogue (4q) demonstrated Kv1.5 activity (IC₅₀ = 600 nM), but decreases in microsomal stability (t_{1/2} = 3 min) and increased inhibition of Cyp 3A4 (90% at 3 μM) were observed.

Table 3. Modified Sulfonyl Hydrazide, **4g**,n-q

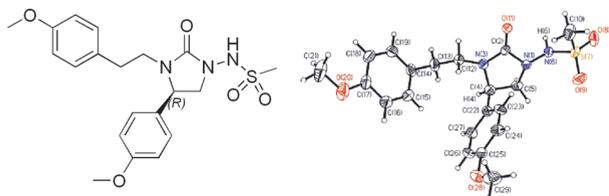
	IW IC ₅₀ (nM)					Cyp 3A4, % inhib at 3 μM ^c
	R ₃	Kv1.5 ^a	hERG ^b	aq sol ^c (μg/mL)	stability (t _{1/2} min) ^d	
4g	(R)-Me	480 ± 44	15100	65	30	45
4n	Bn	340 ± 90	4400	1	3	82
4o	CH ₂ CN	230 ± 50	33000	100	21	7
4p	CH ₂ F	900 ± 222	28300	100	13	0
4q	CH ₂ -3-Py	600 ± 160	ND	23	3	90

^aKv1.5 IC₅₀ determined on an IonWorks platform with CHO-hKv1.5. ^bhERG IC₅₀ values were obtained from Essen Instruments Inc. ^cpH 7.4 buffer, direct UV method. ^dHuman liver microsomal. ^eFluorescent method.¹⁶

Table 4. In Vitro Pharmacology of **4g**

IW IC ₅₀ (nM) ^a		EP IC ₅₀ (μM) ^b					
Kv1.5	hERG	Nav1.5	Cav1.3	Cav1.2	Kv1.1	Kv1.3	Kv4.3
480	15100	> 30	23.4	> 30	2.66	1.41	3.87

^aKv1.5 IC₅₀ determined on an IonWorks platform with CHO-hKv1.5. hERG IC₅₀ values were obtained from Essen Instruments Inc. ^bEP IC₅₀ values were determined with the following stably transfected cell lines: CHO-Nav1.5, HEK-Cav1.3, HEK-Cav1.2, CHO-Kv1.1, CHO-Kv1.3, CHO-Kv4.3.

**Figure 3.** Single crystal X-ray structure of KVI-020, **4g**.

(R)-1-(Methylsulfonylamino)-3-[2-(4-methoxyphenyl)ethyl]-4-(4-methoxyphenyl)-2-imidazolidinone (**4g**) was chosen for further evaluation because of its Kv1.5 potency (IC₅₀ = 480 nM), hERG selectivity (31 fold), and pharmaceutical properties. Compound **4g** was selective against hERG, Nav1.5, Cav1.2, and Cav1.3 but was less selective for homologous channels Kv1.1, Kv1.3, and Kv4.3 (Table 4). The structure of **4g** was confirmed by single crystal X-ray analysis (Figure 3).

The druglike properties of **4g** were examined (Table 5). Dog microsomal stability was lower than human (t_{1/2} of 11 vs 30 min), and the reversible inhibition of Cyp450s 3A4, 2D6, and 2C9 in human liver microsomes was > 37 μM. Caco-2 permeability was high (A-B and B-A = 40 and 39 × 10⁻⁶ cm/s), and substrate efflux was not observed. Beagle and human protein binding were moderate.

The pharmacokinetics of **4g** were evaluated in male beagles at 3 mg/kg iv and 3 mg/kg po (Table 6). A single 30 min iv infusion of **4g** (3 mg/kg) demonstrated moderate clearance (23 (mL/min)/kg), moderate volume of distribution (2.2 L/kg),

Table 5. Selected ADME Properties of **4g**

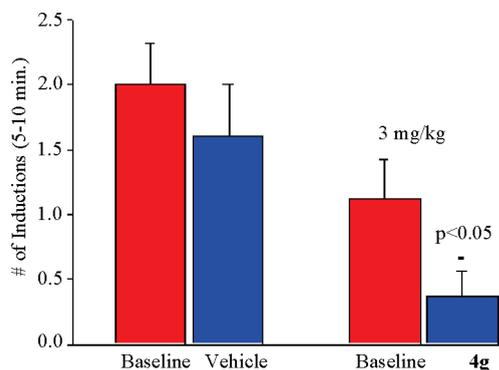
microsomal stability (t _{1/2} min) ^a		Cyp450, IC ₅₀ (μM) ^b			Caco-2 (10 ⁻⁶ cm/s) ^f		plasma protein binding (%) ^g	
dog	human	3A4 ^c	2D6 ^d	2C9 ^e	A-B	B-A	beagle	human
11	30	37	180	47	40	39	90	94
		38						

^a1 μM substrate (**4g**) in 1 mg/mL male beagle dog or male human liver microsomal protein. ^bReversible inhibition in human liver microsomes (0.2 mg/mL) with probe substrates. ^cSubstrates = 2.5 μM midazolam and 50 μM testosterone. ^dSubstrate = 10 μM bufuralol. ^eSubstrate = 10 μM diclofenac. ^f[³H]WYE-160020 (500 ng/mL) determined by equilibrium dialysis in male beagle dog or male human plasma. ^gpH 7.4, bidirectional transport from A to B and from B to A.

Table 6. Beagle Pharmacokinetics of **4g**

dose = 3 mg/kg, iv ^a		dose = 3 mg/kg, po ^b	
parameter		parameter	
Cl _p ((mL/min)/kg)	23	C _{max} (ng/mL)	469
V _{ss} (L/kg)	2.2	T _{max} (h)	1
t _{1/2} (h)	1.2	t _{1/2} (h)	1.7
AUC (ng·h/mL)	2412	AUC (ng·h/mL)	1989
		bioavailability F (%)	82

^aDMAC/PEG200, 10/90, 1 mL/kg. ^b2% Tween/0.5% MC, 3 mL/kg.

**Figure 4.** Compound **4g** reduced the average number of successful AF/AFL inductions per dog that lasted between 5 and 10 min (1.1 ± 0.3 vs 0.4 ± 0.2; *p* = 0.047, *n* = 8; 3 mg/kg).

and a short elimination half-life (1.2 h). Oral pharmacokinetics were characterized by a bioavailability of 82%, a half-life of 1.7 h, and a systemic exposure (AUC) of 1989 ng·h/mL.

The in vivo efficacy of **4g** was then evaluated in several animal models. Prolongation of the atrial effective refractory period (AERP) is a marker of antiarrhythmic activity, while prolongation of the ventricular effective refractory period (VERP) is an indicator of hERG liability.¹⁷ Compound **4g** was evaluated in a beagle model of AERP, and 12% and 17% AERP prolongations were observed at 4.6 and 23 μM steady state plasma concentrations (1.9 and 6.3 mg/kg, iv infusion). VERP remained unchanged in both models, consistent with the desired atrial selectivity. Overall cardiac function, including HR, BP, and dp/dt, was not statistically different between treatment groups and vehicle control.

4g was also evaluated in a canine model of AF, designed to measure incidence of AF in a more clinically relevant setting. In the canine atrial/ventricular tachypacing model,¹⁸ surgical implantation of a pacemaker was followed by 2 weeks of high atrial and ventricular pacing (220 bpm). This induced remodeling of the heart resulted in heart failure characterized as

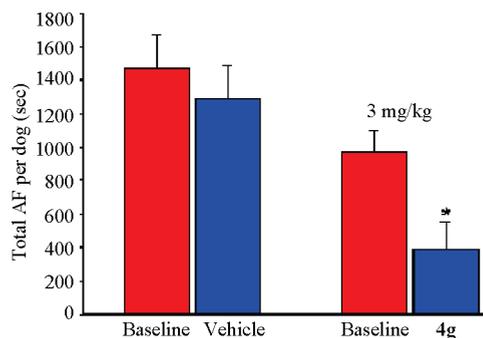


Figure 5. Compound **4g** reduced mean AF/AFL duration per dog (874 ± 122 s vs 393 ± 166 s; $p = 0.033$; 3 mg/kg).

clinically relevant to the human condition. AF was induced via burst pacing (10 s, 600 bpm). Following oral administration of **4g** ($n = 8$, 3 mg/kg), the success rate of inducing AF for 5–10 min intervals decreased 63% (Figure 4), average AF duration decreased 55% (Figure 5), and total AF burden (total time in AF) decreased 52%.

In summary, **4g** is a potent, selective blocker of the atrial potassium channel Kv1.5. It demonstrated efficacy in clinically relevant models of AF and mechanistic models of the cardiac action potential. In addition, its pharmacokinetic and pharmaceutical properties were acceptable for late stage pre-clinical development, and KVI-020/WYE-160020 (**4g**) has been advanced into development for the treatment of AF.

Acknowledgment. The authors thank the Department of Analytical Chemistry group at Wyeth Research for support of the studies described.

Supporting Information Available: Details of the synthesis and characterization of **4a–q**: protocols for in vitro and in vivo experiments. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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